NTP
National Toxicology Program

# Report on the Peer Review of the RoC Draft Monograph on Cobalt and Certain Cobalt Compounds


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NTP Board of Scientific Counselors
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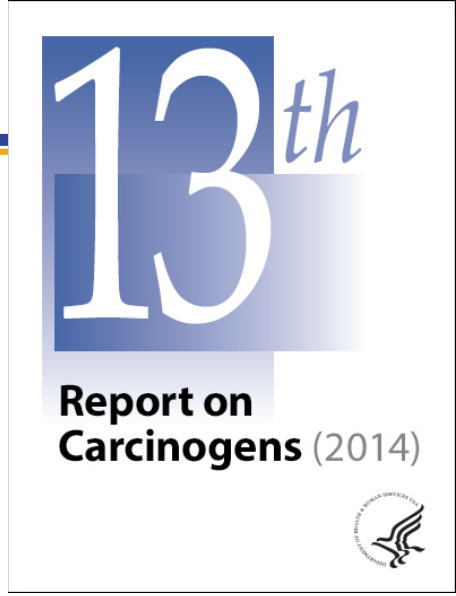
## Outline

- Report on Carcinogens (RoC)
- Cancer hazard evaluation of cobalt
- Peer-review meeting and reports
- NTP conclusions
- Panel comments
- New gentoxicity studies
- Next steps

# The Report on Carcinogens (RoC) is congressionally mandated

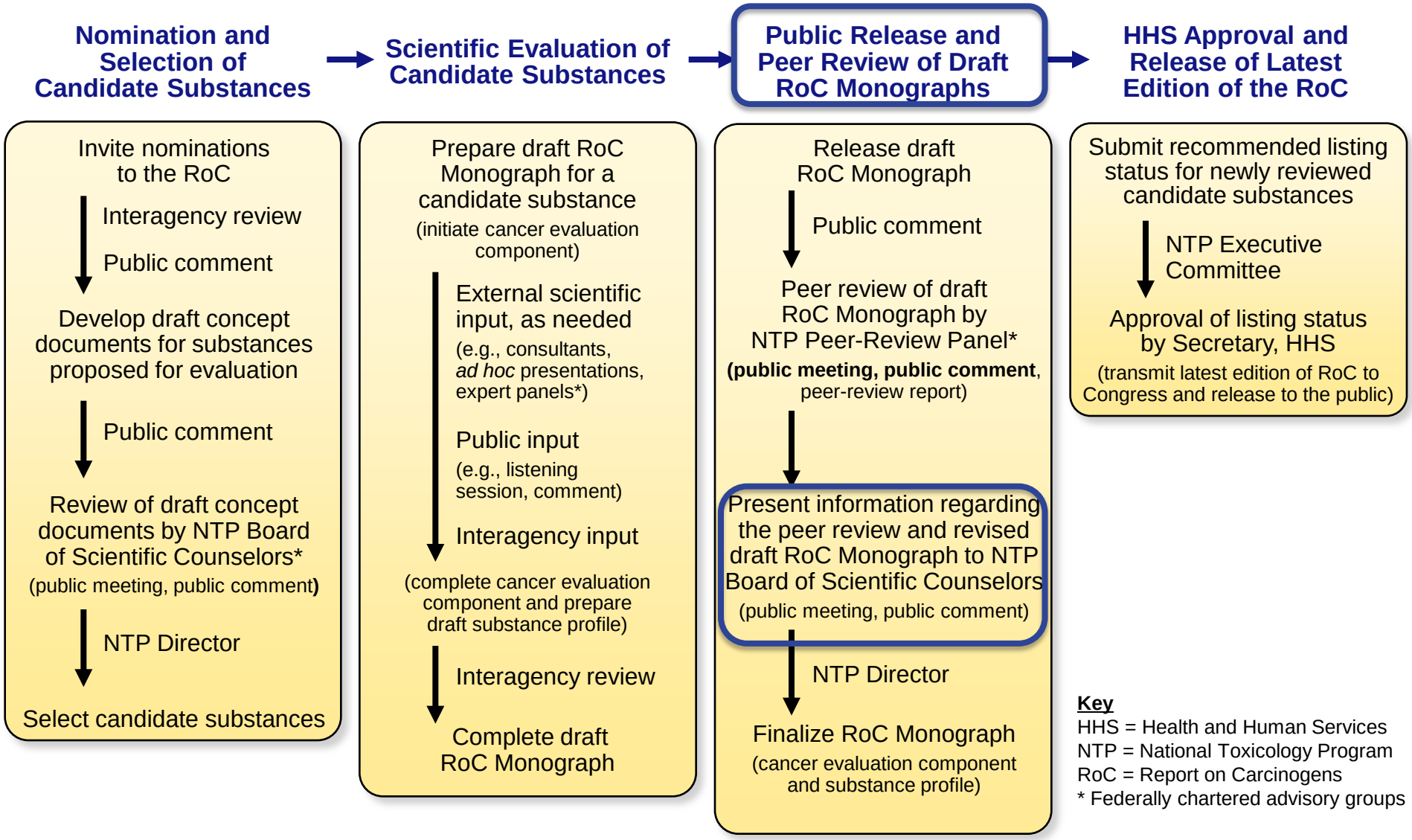



- Public Health Service Act, Section 301(b)(4) (1978, amended 1993)
  - Directs Secretary, Health and Human Services (HHS) to publish a list of carcinogens
  - Lists substances as "*known*" or *"reasonably anticipated human carcinogens"*
- Identifies substances that pose a cancer hazard for people in the United States
- NTP prepares the RoC for the Secretary, HHS
- Each edition of the report is cumulative

http://ntp.niehs.nih.gov/go/roc

# NTP process for preparing the RoC

## Current status in cobalt review



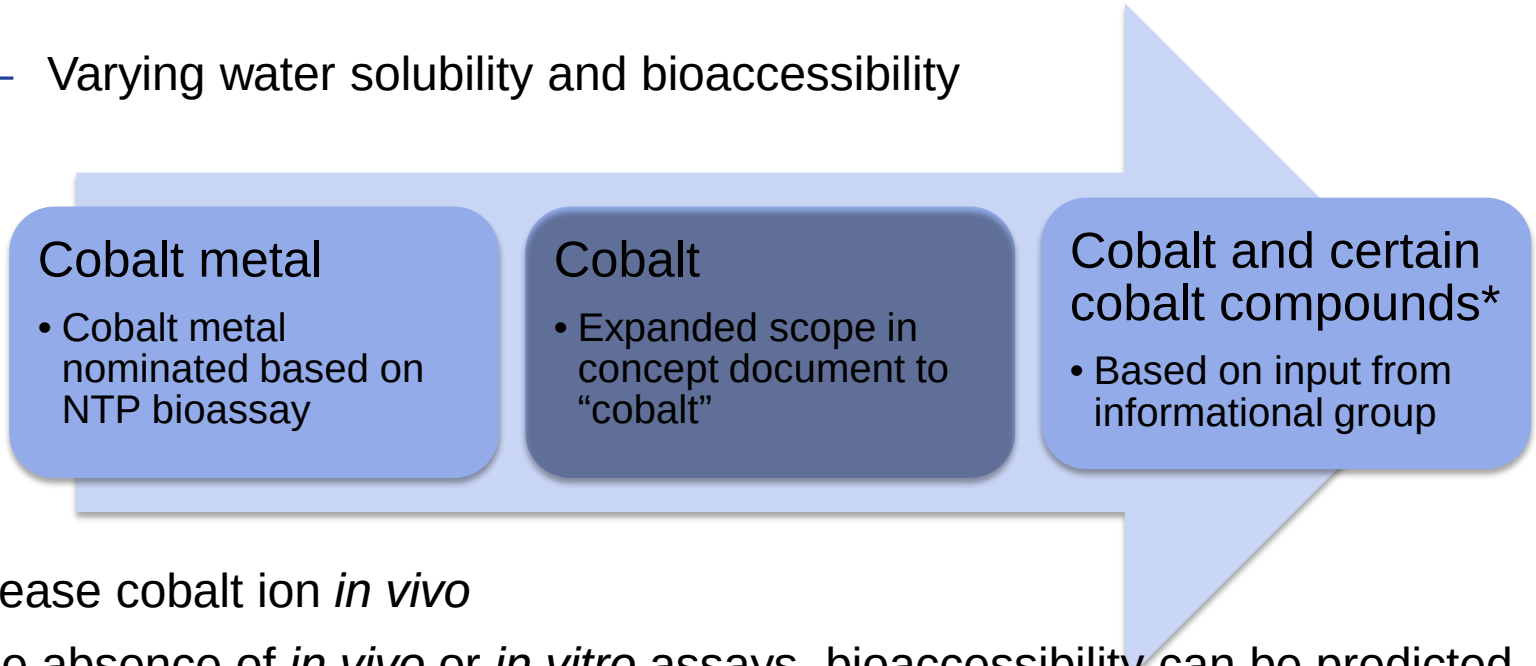

**Key**
HHS = Health and Human Services
NTP = National Toxicology Program
RoC = Report on Carcinogens
* Federally chartered advisory groups

# Defining the candidate substance

## From cobalt metal to a class of cobalt forms

Cobalt is a naturally occurring metallic element that exists in different forms

- Cobalt compounds exist in different valence states, and as inorganic or organic forms
- Varying water solubility and bioaccessibility




*Release cobalt ion *in vivo*

In the absence of *in vivo* or *in vitro* assays, bioaccessibility can be predicted by solubility in artificial biological fluids

Class does not include Vitamin B12, which does not release ions *in vivo*

# Cobalt and cobalt compounds

## Significant exposure to cobalt from both occupational and non-occupational sources

### Metallurgical uses (> 62%)

- Superalloys and other alloys
- Medical such as joint implants

### Chemical uses (27%)

- Pigments, driers, catalysts, adhesives
- Animal diets

### Cemented carbides and bonded diamonds (9%)

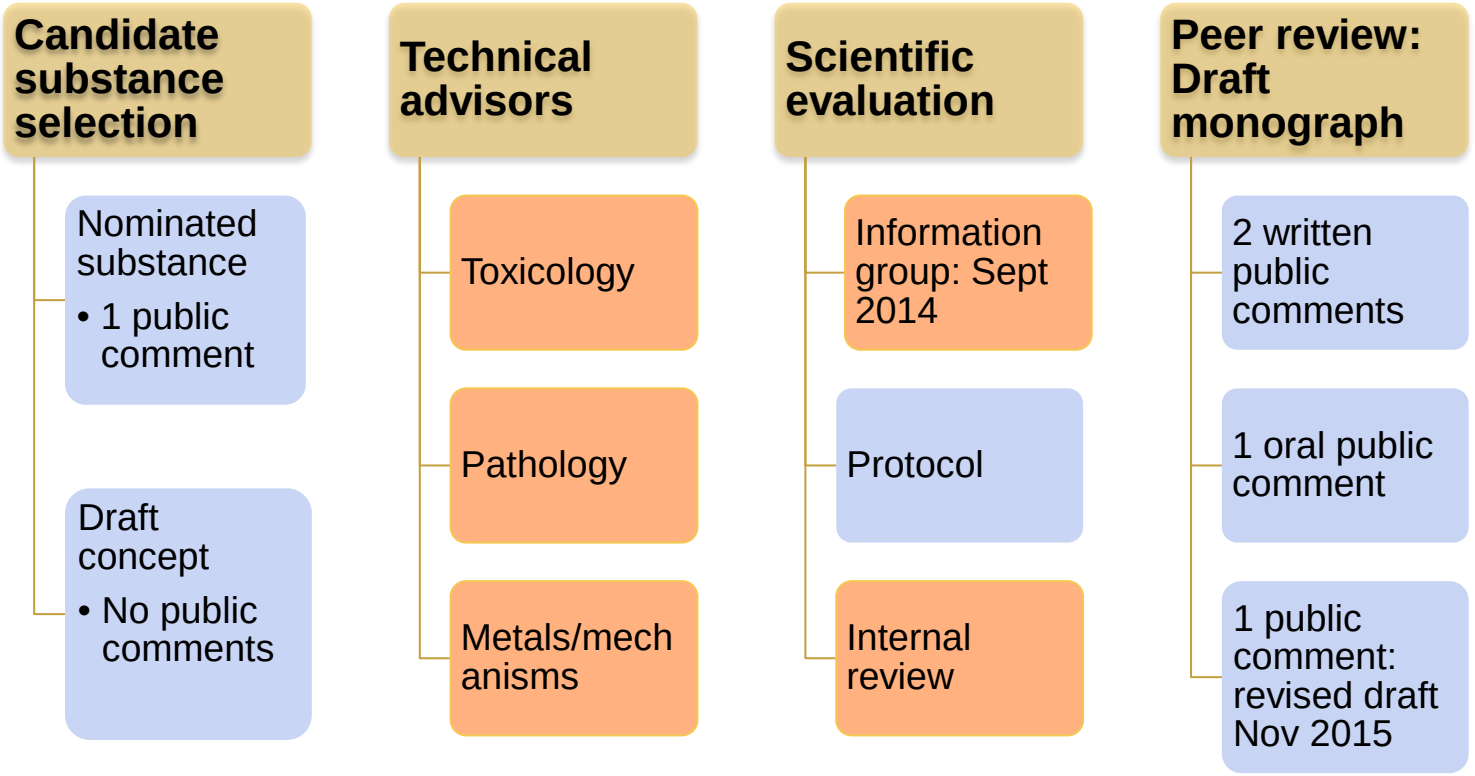
- Tungsten carbides (“hard metals”)
- Steel with microdiamonds impregnated into surface cobalt layer

### Electronics and green energy (< 1%)

- Rechargeable batteries (computers, mobile phones, vehicles)

# Development and review of the draft monograph

## Scientific input and public comments




Time was set aside at the peer-review meeting to discuss scientific issues raised in the public comments.

# Cobalt peer-review panel

| Member | Affiliation |
|---|---|
| Melissa A. McDiarmid, MD, MPH, DABT (Chair) | University of Maryland School of Medicine |
| Lisa De Roo, MPH, PhD | University of Bergen |
| Robert F. Herrick, SD | Harvard School of Public Health |
| C. William Jameson, PhD | CWJ Consulting, LLC |
| John LaPres, PhD | Michigan State University |
| Clark Lantz, PhD | The University of Arizona |
| Marie-Elise Parent, PhD | Université du Québec |
| Michael V. Pino, DVM, PhD, DACVP | Consultant, Veterinary Toxicological Pathology and Preclinical Drug Development |
| John Pierce Wise, Sr., PhD | University of Louisville |
| Anatoly Zhitkovich, PhD | Brown University |

NTP BSC liaison: George B. Corcoran

# Peer-review meeting

| | |
|---|---|
| Charge | To comment on the draft cancer evaluation component, specifically, whether it is technically correct and clearly stated, whether the NTP has objectively presented and assessed the scientific evidence, and whether the scientific evidence is adequate for applying the listing criteria |
| | To comment on the draft substance profile, specifically, whether the scientific justification presented in the substance profile supports the NTP's preliminary policy decision on the RoC listing status of cobalt and certain cobalt compounds |
| Actions (votes) | Whether the scientific evidence supports the NTP's conclusions on the level of evidence for carcinogenicity from cancer studies in humans and experimental animals of cobalt and certain cobalt compounds |
| | Whether the scientific evidence supports the NTP's preliminary listing decision for cobalt and certain cobalt compounds in the RoC |

# Post peer-review steps

## Monograph revised based on Panel comments

**Peer-review report**

- Recommendations on NTP draft conclusions
- Scientific and technical peer-review comments

**NTP response to the peer-review report**

- Responses to comments
- Rationale for accepting/not accepting peer-review recommendations

**Revised draft monograph**

- Revised based on NTP review of peer-review comments

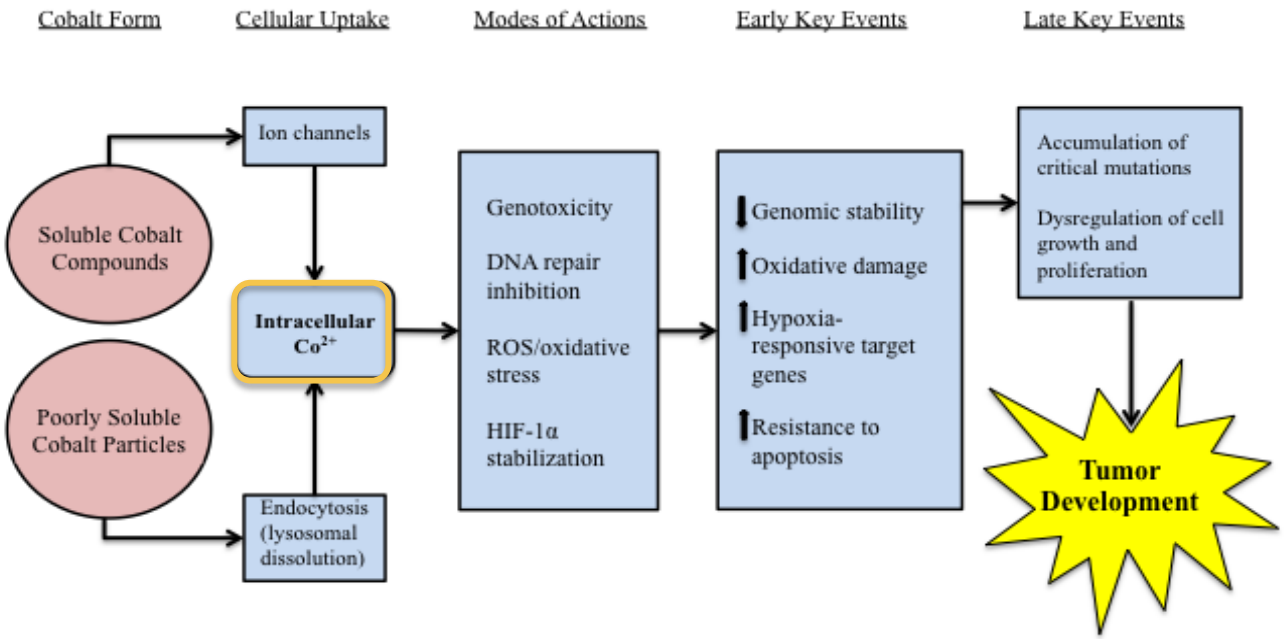
# The Panel agreed with draft NTP conclusions

| Evidence stream | NTP draft recommendation | Panel |
|---|---|---|
| Human cancer studies | Data are inadequate to evaluate the relationship between exposure to cobalt and cancer | Agreed |
| Cancer studies in experimental animals | Sufficient evidence | Agreed |
| Mechanistic data | Mechanisms of carcinogenicity of cobalt and cobalt compounds involves cobalt ion | Agreed |
| Listing recommendation | *Reasonably anticipated to be a human carcinogen** | Agreed |

*Recommended that definition of certain compounds, release cobalt ion *in vivo*, be part of the listing

# Rationale for grouping as a class

## Cobalt ion is proposed to be key in pathways of carcinogenicity



# Rationale for listing cobalt as a class

## Cobalt metal and compounds cause similar biological effects associated with carcinogenicity

| Endpoint | Soluble cobalt salts | | Cobalt metal | Poorly soluble cobalt compounds |
|---|---|---|---|---|
| | $CoCl_2$ | $CoSO_4$ | Particles | CoO or $Co_3O_4$ |
| Bioacessibility | | | | |
| Lysosome* | + | + | + | + |
| Gastric | + | + | + | + |
| Cellular uptake | + | + | + | + |
| Cytotoxicity | + | + | + | + |
| ROS | + | ND | + | + |
| HIF-1α stabilization | + | + | + | + |
| DNA repair inhibition | + | ND | + | ND |
| Genotoxicity *in vitro* | + | + | + | + |
| Genotoxicity *in vivo* | + | ND | – | ND |

ND = no data

* Dissolution of cobalt particles in lysosomal fluid is a key component for the proposed mechanisms

# Similar carcinogenic effects

## Sufficient evidence of carcinogenicity from studies in experimental animals

| Animal Neoplasms | Soluble cobalt salts | | Cobalt metal* | Poorly soluble cobalt compounds |
|---|---|---|---|---|
| | $CoCl_2$ | $CoSO_4$ | particles | CoO |
| Lung | ND | + | + | + |
| Adrenal gland | ND | + | + | ND |
| Injection site | + | ND | + | + |

ND = no data

* Cobalt metal

- Pancreatic islet tumors (exposure related)
- Mononuclear cell leukemia (exposure related)
- Kidney tumors (equivocal)

# Panel's comments on the draft monograph

## Scientific and technical comments to improve the quality of the monograph or other conclusions

- Cobalt clastogenic but not mutagenic
- No scientific disagreements with NTP major conclusions
  - Specific comments addressed in the response document
- Cobalt-containing joint implants (vote)
  - Recommended NTP review the literature on human cancer studies
  - Convene another peer review if relevant data that might change the evaluation were identified

# NTP assessment of implant studies

## Joint implant studies are not informative for evaluating effects of cobalt *per se*

- Studies identified by literature search
  - 30 case reports that specifically mentioned a tumor (malignant fibrous histiocytoma, sarcoma, NHL) at site of cobalt-containing implant; rare occurrence
  - 16 cohort studies and 1 patient series
- Limitations of studies for evaluating cobalt
  - Study design (e.g., case reports)
  - Lack of specificity (other types of implants or metals)
  - Limited sensitivity and inadequate information on extent of cobalt exposure
  - Underlying comorbidities

# Public comments and new information

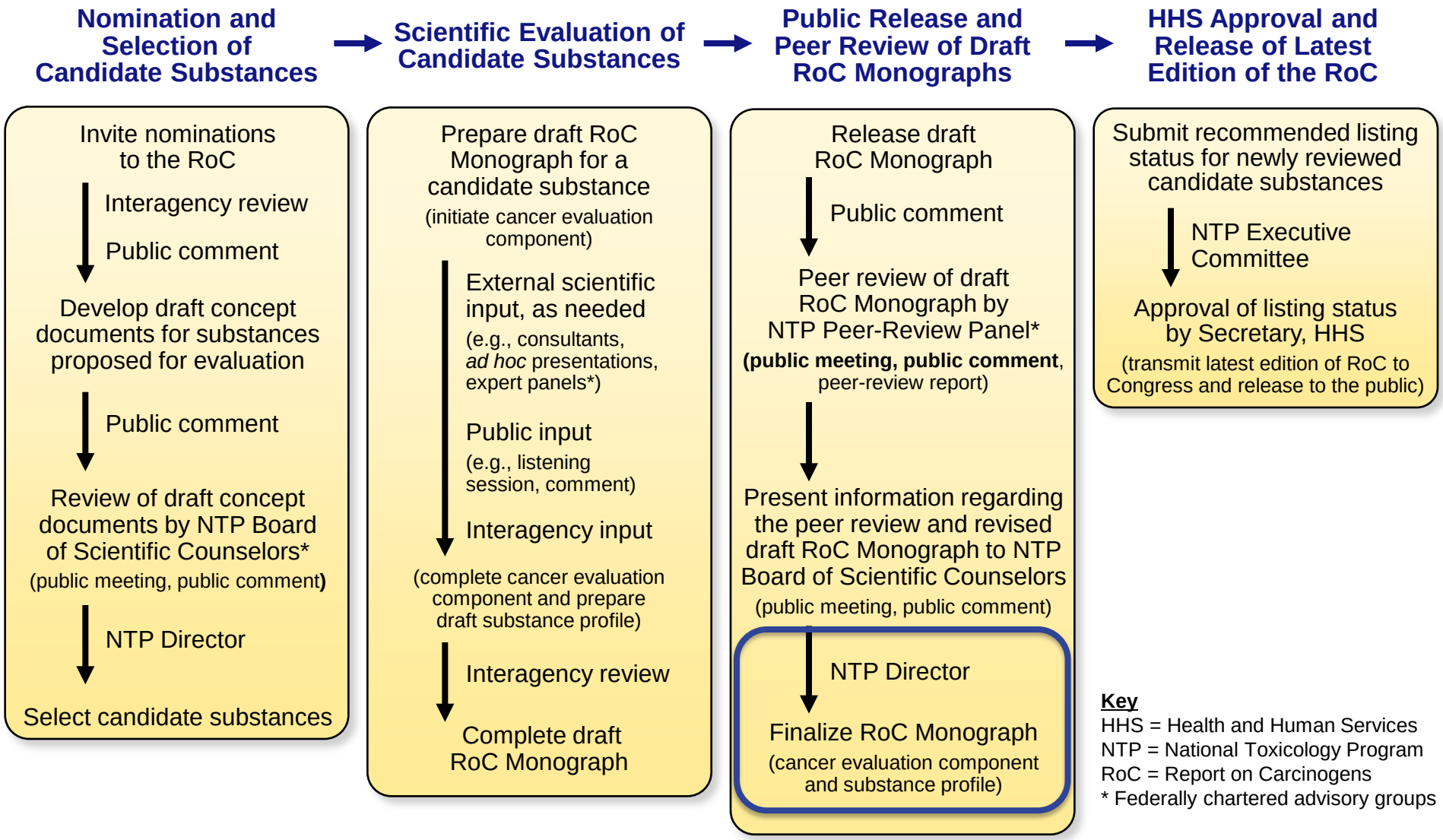
## Cobalt Development Institute (CDI) sponsored genotoxicity studies

- Shared a recently accepted publication of genotoxicity studies (Kirkland *et al.* 2015)
  - NTP and the panel did not review the data at the meeting because of inadequate time, given the size (over 100 pages) and proximity to the meeting (2 days)
  - CDI presented an overview of the findings at the meeting
- Project consisted of over 40 genotoxicity studies
  - Provided genotoxicity information for “new” compounds, i.e., not reported on in the peer-review literature (10/16 tested substances)
  - Provided information on mutagenicity for new and previously tested compounds

## New studies unlikely to change NTP conclusions

- Findings of the individual studies are largely consistent with NTP conclusions concerning specific genotoxic endpoints
  - Mostly negative mutagenicity findings in bacteria and mammalian cells
  - Clastogenic in other *in vitro* studies
  - Unclear findings in *in vivo* studies
- Little impact on rationale for listing cobalt compounds as a class or biological plausibility of the mechanisms of carcinogenicity
- Discussed in NTP response to the peer-review report but not in revised monograph

# Process for preparation of the RoC

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# Acknowledgements


## Office of the RoC

Gloria Jahnke

Diane Spencer (co-project leader)

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Ella Darden

Andrew Ewens

Jessica Geter

Alton Peters

Tracy Saunders

Pam Schwingl

## Peer-Review Panel

## NIEHS and Interagency Scientists: Internal Review

## Technical Advisors and Information Group Members

Mamta Behl, PhD, DABT (Information Group Moderator)

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Arun Pandiri, PhD, DACVP

Matthew Stout, PhD, DABT

Erik Tokar, PhD

John Wheeler, PhD, DABT (ATSDR/CDC)

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# Questions